

## ABSTRACT OF THE DISCLOSURE

The invention provides truncated GSK3 polypeptides capable of crystallization, including GSK3 $\alpha$  and GSK3 $\beta$  polypeptides, and use of these polypeptides to identify and optimize GSK3 inhibitors. Also provided are GSK3 polypeptides having at least one substituted amino acid that differs from wild-type GSK3, wherein the substituted amino acid is incapable of being phosphorylated. The invention finds use in providing methods of identifying and optimizing compounds useful for treating diseases mediated by GSK3 activity, including Alzheimer's disease, type 2 diabetes, and inflammation.